REMARKS

Claims 71 and 84 are objected to for reciting an improper dependency. Applicants have amended the clerical error in claims 71 and 84 such that they depend on claim 82 rather than claim 80.

Claims 71, 72, 76-82 and 84 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Akiyama et al. in view of Al-Razzak et al. Applicants disagree and in view of the following remarks request that the Examiner reconsider and withdraw the rejection.

Al-Razzak has been cited for disclosure of a tablet comprising 500 mgs of clarithromycin and low-viscosity HPMC in amounts of 100, 200 and 300mg. The Examiner states "As Akiyama teaches that clarithromycin may be delivered by the tablet, any ordinary person would have looked to the art for suitable amounts of clarithromycin for delivering to a subject." However, Applicants' invention is not simply a tablet comprising clarithromycin, but rather a specific controlled release formulation comprising particular components. Applicants' formulation is not suggested by Akiyama alone or in combination with Al-Razzak, and the cited references actually teaches away from Applicants' formulations.

Akiyama has provided extremely broad groups of (1) active agents, (2) polyglycerol fatty acid esters and (3) viscogenic agents, and explicitly teaches that the selection of the proper polyglycerol fatty acid ester is dependent on the particular combinations of the active ingredient, the viscogenic agent, the swelling material (page 10, line 35 to page 11, line 4).

Al-Razzak teaches that adding low viscosity HPMC in its compositions inhibits release of the clarithromycin (see Al-Razzak Figure 1). In contrast, Applicants disclose on page 6, lines 9-18 that in their formulations, the combination of low viscosity HPMC with glyceryl behenate loosens the glyceryl behenate structure and makes possible a release of the clarithromycin. Based on

the teachings of Al-Razzak that combining low viscosity HPMC with clarithromycin *delays* its release and Akiyama's teaching that the selection of the proper polyglycerol fatty acid ester is dependent on the particular combinations of the active ingredient, the viscogenic agent, the swelling material, one of skill in the art based on Akiyama and Al-Razzak would not combine a low viscosity HPMC with glyceryl behenate with the expectation that the HPMC would enhance release of an active agent from the glyceryl behenate. Al-Razzak supports Applicants' position that Akiyama's disclosure is too general and presents too many prior art combinatorial possibilities to render the claimed invention obvious.

In particular, Akiyama is directed to a gastrointestinal mucosa-adherent pharmaceutical composition which generically comprises an active ingredient, a polyglycerol fatty acid ester and a viscogenic agent. And while Akiyama may disclose various amounts of ingredients that are preferred, Akiyama really only provides a general teaching of various components that could be combined in various ways. For example, regarding the active ingredient, Akiyama on page 14, line 11 through page 15, line 15 discloses a laundry list of suitable active ingredients:

> The active ingredient for use in the present invention may be absorbed from gastrointestinal mucosa or expressed its efficacy directly or indirectly in the gastrointestine, such as any anti-HP substance showing activity against strains of microorganism belonging to the genus Helicobacter (particularly Helicobacter pylori) whether directly or indirectly, thus including antimicrobial substance and inhibitors of urease which is known to be indispensable for survival of bacteria of the genus Helicobacter.
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> The antimicrobial substance includes but is not limited to antibiotics in the penicillin series (e.g. amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotics in the cephalosporin series, macrolide antibiotics (e.g. erythromycin, clarithromycin, roxithromycin, azithromycin, etc.), tetracyclines (e.g. tetracycline, minocycline, etc.), aminoglycosides (e.g. gentamicin, amikacin, streptomycin,

> etc.), bismuth salts (e.g. bismuth acetate, bismuth citrate, bismuth salicylate, etc.), imidazoles (e.g. metronidazole, tinidazole, miconazole, etc.), quinolones (e.g. ofloxacin, ciprofloxacin, etc.), and tryptophanyl-t-RNA synthesis inhibitors (e.g. oxazolone derivatives (Preferably indolmycin) etc.). Particularly preferred are penicillins, macrolides, imidazoles, and tryptophanyl-t-RNA synthesis inhibitors. In particular, such as amoxicillin, clarithromycin or indolmycin is preferred.
>
> The urease inhibitor includes but is not limited to hydroxamic acid derivatives (e.g. acetohydroxamic acid and the compounds described or referred to in the above-mentioned Synopsis of Lectures at the 4th Annual Meeting of Medical Chemistry Group), phosphoramide derivatives [e.g. flurofamide (Micro. Ecol. Health Dis. referred to hereinbefore) and phenylphosphorodiamidate compound A (compound of Reference Example 2)), phosphates, thiols (e.g. 2-mercaptoethanol etc.), boric acid, halogen compounds (e.g. fluorides etc.), and cassia bark extract (the above-mentioned Synopsis of Lectures at the 117th Congress of Pharmaceutical Society of Japan).
>
> Page 14, line 11 to page 15, line 15

With respect to the polyglycerol fatty acid ester, Akiyama teaches that the polyglycerol fatty acid ester includes *but is not limited to*:

> ...behenic acid hexa(tetra)glyceride, caprylic acid mono(deca)glyceride, caprylic acid di(tri)glyceride, capric acid di(tri)glyceride, lauric acid mono(tetra)glyceride, lauric acid mono(hexa)glyceride, lauric acid mono(deca)glyceride, oleic acid mono(tetra)glyceride, oleic acid mono(hexa)glyceride, oleic acid mono(deca)glyceride, oleic acid di(tri)glyceride, oleic acid di(tetra)glyceride, oleic acid sesqui(deca)glyceride, oleic acid penta(tetra)glyceride, oleic acid penta(hexa)glyceride, oleic acid deca(deca)glyceride, linoleic acid mono(hepta)glyceride, linoleic acid di(tri)glyceride, linoleic acid di(tri)glyceride, linoleic acid di(tetra)glyceride, linoleic acid di(hexa)glyceride, stearic acid mono(di)glyceride, stearic acid mono(tetra)glyceride, stearic acid penta(tetra)glyceride, stearic acid mono(deca)glyceride, stearic acid tri(tetra)glyceride, stearic acid penta(hexa)glyceride, stearic acid tri(hexa)glyceride, stearic acid deca(deca)glyceride, palmitic acid mono(tetra)glyceride, palmitic acid

> mono(hexa)glyceride, palmitic acid mono(deca)glyceride, palmitic acid tri(tetra)glyceride, palmitic acid tri(hexa)glyceride, palmitic acid sesqui(hexa)glyceride, palmitic acid penta(tetra)glyceride, palmitic acid penta(hexa)glyceride, palmitic acid deca(deca)glyceride, and polyglycerol polyricinolate (e.g. tetraglycerol polyricinolate, etc.).
>
> The preferred polyglycerol fatty acid ester includes, for instance, behenic acid hexa(tetra)glyceride (e.g. HB-31O™, Sakamoto Yakuhin Kogyo Co., Ltd.,; Poem J-46B™, Riken Vitamin Co.), stearic acid penta(tetra)glyceride (e.g. PS-310m, Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid mono(tetra)glyceride (e.g. MS-31O™, Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid penta(hexa)glyceride (e.g. PS-500m, Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid mono(deca)glyceride, polyglycerol polyricinolate (e.g. tetraglycerol polyricinolate, etc.) (e.g. CRS-75™, Sakamoto Yakuhin Co., Ltd.) and mixtures of such glycerides.
>
> Those polyglycerol fatty acid esters can be used each alone or as a mixture of two or more species, preferably about 2 or about 3 species.
>
> Page 9, line 10 to page 10, line 19

And on page 12, which was cited in the Office Action to demonstrate that "the lipids include glycerol fatty acid esters wherein behenic acid is taught as a fatty acid", Akiyama discloses:

> The lipid for use in the present invention is one having a melting point of about 40 to about 120°C, preferably about 40 to about 90°C. The lipid includes but is not limited to saturated fatty acids of about 14 to about 22 carbon atoms (e.g. myristic acid, stearic acid, palmitic acid, behenic acid, etc.) or salts (sodium salt, potassium salt, etc.) thereof; higher alcohols of about 16 to about 22 carbon atoms (e.g. cetyl alcohol, stearyl alcohol, etc.); fatty acid glycerol esters such as the monoglycerides, diglycerides, triglycerides, etc. of the above-mentioned fatty acids (e.g. 1-monostearin, 1-monopalmitin, etc.); oils (e.g. castor oil, cottonseed oil, beef tallow, etc., inclusive of the corresponding hydrogenated oils); waxes (e.g. beeswax, carnauba wax, sperm wax, etc.); hydrocarbons (e.g. paraffin, microcrystalline wax, etc.); and phospholipids (e.g. hydrogenated lecithin etc.). Among those

> lipids, oils, waxes, C_{14-22} saturated fatty acids, C_{16-22} higher alcohols, and hydrocarbons are preferred. The more preferred are hydrogenated cottonseed oil, hydrogenated castor oil, hydrogenated soybean oil, carnauba wax, stearic acid, stearyl alcohol, and microcrystalline wax. The most preferred is hydrogenated castor oil or carnauba wax. When a lipid is used as the gastrointestinal mucosa-adhesive matrix, the amount of the lipid relative to the total weight of the composition is generally about 5 to about 98 weight %, preferably . . . .

With regard to the type of viscogenic agent, Akiyama discloses *any* type of viscogenic agent can be used:

> Any type of viscogenic agent can be used in the present invention as long as it becomes sufficiently viscous with water to attach itself to the gastrointestinal mucosa and is pharmaceutically acceptable. Preferred, however, are those substances which are markedly swollen by water and develop high degrees of viscosity. The viscogenic agent, thus, includes synthetic polymers and naturally-occurring viscogenic materials.
>
> The preferred synthetic polymer is a polymer such that the viscosity of a 2% aqueous solution thereof at 20°C is about 3 to about 50000 cps., preferably about 10 to about 30000 cps., and for still better results, about 15 to about 30000 cps. However, when a basic or an acidic polymer which gains in viscosity on neutralization is used, the preferred polymer is such that the viscosity of a 0.2% solution thereof after neutralization at 20°C is about 100 to about 500000 cps, preferably about 100 to about 200000 cps, and for still better results, about 1500 to about 100000 cps.
>
> The value of the viscosity is measured with a Brookfield viscometer. Preferably the above-mentioned polymer is an acidic polymer which includes but is not limited to carboxyl- or sulfo-containing polymers and the corresponding salt-containing polymers. Particularly preferred are carboxyl-containing polymers and carboxylate salt-containing polymers.
>
> The carboxyl (inclusive of its salt)-containing polymer is preferably an acrylic homopolymer or copolymer containing acrylic acid as a monomer unit or a salt thereof. The salt

includes monovalent metal salts such as the sodium salt, potassium salt, etc. and divalent metal salts such as the magnesium salt, calcium salt, ammonium salt, etc.

The acrylic polymer, inclusive of its salt, includes polymers containing carboxyl groups in a proportion of about 58 to about 63 weight % and having a molecular weight of about 20 x 104 to about 600 x 10^4, preferably about 100 x 10^4 to about 600 x 10^4, and more preferably about 100 x 10^4 to about 500 x 10^4.

The preferred acrylic polymer, inclusive of its salt, includes acrylic acid homopolymers and their salts. Such polymers are listed under the heading of carboxyvinyl polymer in Japanese Standards of Pharmaceutical Ingredients (October 1986).

As specific examples of said acrylic polymer, there can be mentioned carbomer [Carbopolm (hereinafter referred to as Carbopol), The B. F. Goodrich Company] 940, 934, 934P, 941, 1342, 974P, 971P (NF XVIII), EX214 etc., HIVISWAKO™ 103, 104, 105, and 204 (Wako Pure Chemical Industries), NOVEON AA1™ (The B. F. Goodrich Company), and calcium polycarbophil (USP XXIII)). The naturally-occurring viscogenic agent includes but is not limited to mucin, agar, gelatin, pectin, carrageenin, sodium alginate, locust bean gum, xanthan gum, tragacanth gum, chitosan, pullulan, waxy starch, sucralfate, curdlan, and cellulose and its derivatives (cellulose sulfate and preferably hydroxypropylcellulose or hydroxypropylmethylcellulose).

The most preferred viscogenic agent is an acrylic polymer or its salt.

Those viscogenic agents can be used alone or in combination.

Page 17, line 11 to page 4

With regard to the amount of the "*any* viscogenic agent" that can be used in Akiyama's compositions, Akiyama discloses:

Referring to the amount of the viscogenic agent for use in the composition of the invention, its amount in the gastrointestinal mucosa-adherent matrix may for example be about 0.005 to about 99 weight %, preferably about 0.5 to about 45 weight %, more preferably about 1 to about 30 weight %, furthermore preferably about 1 to about 25 weight %, and for still better result, about 1 to about 20 weight %. When, for example, the viscogenic agent is dispersed in a

> matrix comprising the polyglycerol fatty acid ester and/or lipid, the amount of the viscogenic agent is about 0.005 to about 95 weight %, preferably about 0.5 to about 30 weight %, and more preferably about 1 to about 25 weight %, and for still better result, about 1 to about 20 weight % based on the total weight. When the matrix is coated with the viscogenic agent, the proportion of the viscogenic agent is also about 0.005 to about 95 weight %, preferably about 0.5 to about 30 weight %, and more preferably about 1 to about 25 weight %, and for still better result, about 1 to about 20 weight based on the total weight.
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> Page 19, line 5 to line 25

The foregoing demonstrates that Akiyama is expressly teaching that there are a great number of combinatorial possibilities.

Akiyama discloses broad groups of (1) active agents, (2) polyglycerol fatty acid esters and (3) viscogenic agents, and explicitly teaches that the selection of the proper polyglycerol fatty acid ester is dependent on the particular combinations of the active ingredient, the viscogenic agent, the swelling material (page 10, line 35 to page 11, line 4). Al-Razzak teaches that low viscosity HPMC delays release of clarithromycin. Therefore, one of skill in the art in view of Akiyama and Al-Razzak would not combine glyceryl behenate with a low viscosity HPMC with the expectation that the combination would enhance the release of clarithromycin from the glyceryl behenate generating a controlled release formulation as claimed by Applicants. As such, the combination of Akiyama and Al-Razzak does not render Applicants' claimed control release formulation obvious.

In view of the foregoing remarks Applicants request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103 in view of Akiyama and Al-Razzak.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323, Docket No. 104101.B700017.

Respectfully submitted,

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